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(In connection with Application No. 10/762,566)

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(71) Applicant *(for all designated States except US)*: R.P. SCHERER CORPORATION [US/US]; 2301 West Big Beaver Road, Troy, MI 48007-7060 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: SEAGAR, Harry [GB/GB]; Ashley Lodge, Ashley, Box, Corsham, Wiltshire SN14 9AN (GB).

(74) Agent: HITCHCOCK, Esmond, Antony; Lloyd Wise, Tregear & Co., Commonwealth House, 1-19 New Oxford Street, London WC1A 1LW (GB).

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(54) Title: FAST DISSOLVING PHARMACEUTICAL PRODUCTS

(57) Abstract

A dosage form for oral administration comprises a solid, fast-dispersing or fast-dissolving matrix carrying a drug of the kind not generally effectively absorbed after conventional oral ingestion. These drugs are referred to as "non-absorbed drugs". The dosageform provides for rapid release of the drug and its even distribution over mucosal surfaces in the mouth, pharynx and oesophagus. The drug is particularly adapted for absorption at these sites. The fast-dispersing carrier ensures that the drug is irrevocably dispersed in a patient's mouth, and in active contact with these target sites, enabling its absorption pre-gastrically.

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FAST DISSOLVING PHARMACEUTICAL PRODUCTS

This invention relates to pharmaceutical products, and particularly to such products suitable for oral ingestion and capable of rapid disintegration in the oral cavity.

A large variety of dosage forms for oral ingestion are known and readily available. Some such dosage forms are used for the controlled delivery and absorption of medicaments to different sites in the gastro-intestinal tract, the requisite control being achieved by the rate at which the carrier for the medicament breaks down and releases it. Thus, fast dispersing carriers are used for such products in which the medicament is to be quickly released. Slower dispersing carriers and carriers resistant to digestion in the gastro-intestinal tract can be used where it is intended that release of the medicament is to be delayed, for example until the product has itself reached the upper or lower intestine.

Some drugs are administered orally in the form of a tablet designed to be swallowed whole or a measured amount of a conventional syrup designated to be swallowed rapidly. Drugs administered in this way are absorbed from the gastrointestinal tract, that is, the stomach, the small intestine and the proximal large intestine (colon), into the hepatic portal system and are presented to the liver before reaching the systemic circulation. The liver is known to be the principal site for conversion of drugs into metabolites, some of which are unwanted. Consequently, this first pass of absorbed drug through the liver results in extensive metabolism of the drug and a significant proportion of the absorbed dose never reaches the systemic circulation. This phenomenon is known as the "first pass effect" and results in a decrease in the bioavailability of drugs administered in this way (see Heinonen et al, Clinical Pharmacology & Therapeutics,

Vol. 56, No. 6, (1994), pp. 742-749).

Certain drugs are hydrophobic and exhibit poor bioavailability when taken orally. Some other drugs, and particularly peptide and proteinaceous drugs, mucopolysaccharides, carbohydrates and lipids, are unsuitable for conventional oral delivery for the reason that they would be subject to cleavage by acids and enzymes in the gastrointestinal tract prior to absorption. The present invention is concerned particularly with such drugs; ie, those not generally effectively absorbed after conventional oral ingestion. These drugs will be referred to hereinafter as "non-absorbed drugs".

The aim of the present invention is to provide a means by which non-absorbed drugs can be taken orally, and targeted to appropriate sites to obtain their absorption pre-gastrically. The target sites for drugs provided in dosage forms according to the invention are the mucosal surfaces in the mouth, pharynx and oesophagus. If a drug can achieve absorption at the pre-gastric target sites, then it avoid the destructive "first pass" via the liver. By achieving pre-gastric absorption they also avoid the stomach, and go straight to the circulatory tissue.

According to the invention, a dosage form comprises a solid, fast-dispersing or fast-dissolving matrix carrying a non-absorbed drug. This form provides for rapid release of the drug and its even distribution over the target sites. The drug is particularly adapted for absorption at these sites. The adapted drug can be borne in a fast-dispersing carrier, thereby taking advantage of such carriers, and ensuring that the drug is irrevocably dispersed in a patient's mouth, and in active contact with the target sites.

There are various means by which non-absorbed drugs can be adapted for pre-gastric absorption. A principal step in one such adaptation is to provide the drug in

particulate form, and with a very low average particle size. In such embodiments of the invention a typical maximum particle size is 400 nanometers, although an average particle size of no greater than 100 nanometers would be preferred. The particle surfaces may themselves be modified to improve the bioavailability of the drug, and examples of means by which the particle surfaces can be so modified are given in PCT Patent Publication Nos. WO93/25190; WO96/22766; WO96/25921; and WO97/04756. The nanoparticle technology disclosed in these publications provides means by which the bioavailability of the drugs disclosed can be improved. We have found that by providing them in a dosage form comprising a fast-dispersing or fast-dissolving matrix, the adapted drug can disperse more uniformly and rapidly in the mouth and promote pre-gastric absorption.

Another means by which drugs can be adapted for use in dosage forms according to the invention, is encapsulation in proteinoid microspheres. This microsphere technology is itself known, and reference is directed to U.S. Patent No. 5540939, and PCT Publication Nos. WO94/23702; WO94/28878; and WO96/09813. This microsphere encapsulation option can also be taken up when the drug is provided in nanoparticulate form, as described above.

A third option for adapting drugs for incorporation into dosage forms of the invention is to convert the drug into a form which has better absorption characteristics, the drug adapting after the converted form has been absorbed, thereby releasing the drug at the target sites in its native form. Typically, the converted form is an intermediate conformational state between its native and denatured state, in a supramolecular non-covalently bonded complex. Certain drugs can be so converted by exposure to a complexing perturbant, as is described in PCT Publication No. WO96/12475, to which once again, reference is directed.

This option has the additional advantage that in its converted form the drug can be more stable and better resist enzymatic degradation.

Coated microemulsions or microemulsion preconcentrates or liposomes can also be used to protect drugs from enzymatic degradation, and/or to enhance absorption of the drug in the target sites. It is preferred that dosage forms of the invention disintegrate within 1 to 60 seconds, more preferably 1 to 30 seconds, especially 1 to 10 seconds and particularly 2 to 8 seconds, of being placed in the oral cavity.

With the rapid and frequent clearance of material from the gastrointestinal tract also being a factor, drugs and dosage forms according to the invention will also normally include a mucoadhesive element or substance. Mucoadhesive technology is well established, and some suitable polymeric mucoadhesives are disclosed in PCT Publication No. WO94/20070.

Fast-dispersing dosage forms, delivered orally, have been demonstrated to rapidly disperse and coat the mucosal surfaces in the mouth, pharynx and oesophagus. In this respect reference is directed to a paper by Wilson et al published in the International Journal of Pharmaceutics, 40 (1997) pages 119-123. Figure 1 in that paper shows the results of a gamma scintigraphic study. Dosage forms which dissolve rapidly in saliva, without the aid of water, have also been demonstrated to increase the time in which the rapidly dispersed contents are in contact with the target sites within the buccopharyngeal area and increase the time taken to reach the stomach, when compared to tablets and capsules. Reference is directed to a further paper by Wilson et al published in the International Journal of Pharmaceutics, 46 (1998) pages 241-246); see particularly Figure 1.

Reference is also directed to a paper by Burton et

al published in J. Pharm. Pharmacol 1995. Vol 47, pp 901 - 906. The paper considers the effects of drug adaptation and particular dosage forms on the retention of the respective drug in the oesophagus and in the stomach.

The use of a fast-dispersing dosage form, delivered orally, improves the targeting of drugs to mucous membranes in the mouth, the pharynx and the oesophagus and in turn, the concentration of drug making contact with these tissues. Fast-dispersing dosage forms increase the contact time with the target tissue in the buccopharyngeal and oesophagal area. Furthermore, where drugs are appropriately protected from digestion in the stomach and gut, rapidly dispersed materials will further promote absorption of any drug which reaches the small intestine.

One example of a fast-dispersing dosage form is described in U.S. Patent No. 4855326 in which a melt spinnable carrier agent, such as sugar, is combined with an active ingredient and the resulting mixture spun into a "candy-floss" preparation. The spun "candy-floss" product is then compressed into a rapidly dispersing, highly porous solid dosage form.

U.S. Patent No. 5120549 discloses a fast-dispersing matrix system which is prepared by first solidifying a matrix-forming system dispersed in a first solvent and subsequently contacting the solidified matrix with a second solvent that is substantially miscible with the first solvent at a temperature lower than the solidification point of the first solvent, the matrix-forming elements and active ingredient being substantially insoluble in the second solvent, whereby the first solvent is substantially removed resulting in a fast-dispersing matrix.

U.S. Patent No. 5079018 discloses a fast-dispersing dosage form which comprises a porous skeletal structure of a water soluble, hydratable gel or foam forming

material that has been hydrated with water, rigidified in the hydrated state with a rigidifying agent and dehydrated with a liquid organic solvent at a temperature of about 0°C or below to leave spaces in place of hydration liquid.

Published International Application No. WO 93/12769 (PCT/JP93/01631) describes fast-dispersing dosage forms of very low density formed by gelling, with agar, aqueous systems containing the matrix-forming elements and active ingredient, and then removing water by forced air, vacuum drying, or other drying systems.

U.S. Patent No. 5298261 discloses fast-dispersing dosage forms which comprise a partially collapsed matrix network that has been vacuum-dried above the collapse temperature of the matrix. However, the matrix is preferably at least partially dried below the equilibrium freezing point of the matrix.

U.S. Patent No. 5587180 discloses a particulate support matrix for a tablet, and method for making same, which disintegrates or dissolves in just a few seconds once placed in the oral cavity. The particulate support matrix comprises a first polymeric component which may be a polypeptide, a second polymeric component which may be a different polypeptide, and may be a hydrolyzed gelatin, and a bulking agent.

Published International Application No. WO 91/04757 (PCT/US90/05206) discloses fast-dispersing dosage forms which contain an effervescent disintegration agent designed to effervesce on contact with saliva to provide rapid disintegration of the dosage form and dispersion of the active ingredient in the oral cavity.

The term "fast-dispersing dosage form" therefore encompasses all the types of dosage form described in the preceding paragraphs. However, it is particularly preferred that the fast-dispersing dosage form is of the type described in U.K. Patent No. 1548022, that is, a solid fast-dispersing dosage form comprising a network

of the active ingredient and a water-soluble or water-dispersible carrier which is inert towards the active ingredient, the network having been obtained by subliming solvent from a composition in the solid state, that composition comprising the active ingredient and a solution of the carrier in a solvent.

In the case of the preferred type of fast-dispersing dosage form described above, the composition will preferably contain, in addition to the active ingredient, matrix forming agents and secondary components. Matrix forming agents suitable for use in the present invention include materials derived from animal or vegetable proteins, such as the gelatins, dextrins and soy, wheat and psyllium seed proteins; gums such as acacia, guar, agar, and xanthan; polysaccharides; alginates; carboxymethylcelluloses; carrageenans; dextrans; pectins; synthetic polymers such as polyvinylpyrrolidone; and polypeptide/protein or polysaccharide complexes such as gelatin-acacia complexes.

Other matrix forming agents suitable for use in the present invention include sugars such as mannitol, dextrose, lactose, galactose and trehalose; cyclic sugars such as cyclodextrin; inorganic salts such as sodium phosphate, sodium chloride and aluminium silicates; and amino acids having from 2 to 12 carbon atoms such as a glycine, L-alanine, L-aspartic acid, L-glutamic acid, L-hydroxyproline, L-isoleucine, L-leucine and L-phenylalanine.

One or more matrix forming agents may be incorporated into the solution or suspension prior to solidification. The matrix forming agent may be present in addition to a surfactant or to the exclusion of a surfactant. In addition to forming the matrix, the matrix forming agent may aid in maintaining the dispersion of any active ingredient within the solution or suspension. This is especially helpful in the case

of active agents that are not sufficiently soluble in water and must, therefore, be suspended rather than dissolved.

Secondary components such as preservatives, antioxidants, surfactants, viscosity enhancers, colouring agents, flavouring agents, pH modifiers, sweeteners or taste-masking agents may also be incorporated into the composition. Suitable colouring agents include red, black and yellow iron oxides and FD & C dyes such as FD & C blue No. 2 and FD & C red No. 40 available from Ellis & Everard. Suitable flavouring agents include mint, raspberry, liquorice, orange, lemon, grapefruit, caramel, vanilla, cherry and grape flavours and combinations of these. Suitable pH modifiers include citric acid, tartaric acid, phosphoric acid, hydrochloric acid and maleic acid. Suitable sweeteners include aspartame, acesulfame K and thaumatic. Suitable taste-masking agents include sodium bicarbonate, ion-exchange resins, cyclodextrin inclusion compounds, adsorbates or microencapsulated actives.

CLAIMS

1. A solid unit oral dosage designed to disperse rapidly in the mouth, comprising a matrix carrying a non-absorbed drug form (as herein defined) adapted for pre-gastric absorption.

2. A dosage form according to Claim 1 wherein the non-absorbed drug is one of an hydrophobic drug, a peptide, and a proteinaceous drug.

3. A dosage form according to Claim 1 or Claim 2 wherein the drug is in particulate form with an average particle size no greater than 400 nanometers.

4. A dosage form according to Claim 3 wherein the surfaces of the particles have been modified to improve the bioavailability of the drug.

5. A dosage form according to Claim 4 wherein the surface modifier comprises a block copolymer.

6. A dosage form according to Claim 5 wherein the block copolymer is linked to at least one ionic group.

7. A dosage form according to Claim 5 wherein the block copolymer contains at least one polyoxyethylene block and at least one polyoxy (higher alkaline) block.

8. A dosage form according to Claim 7 wherein at least some of the blocks are linked by an oxymethylene linking group.

9. A dosage form according to Claim 1 or Claim 2 wherein the drug is encapsulated in proteinoid microspheres.

10. A dosage form according to Claim 9 wherein the proteinoid microspheres include an amine reactive modifying agent.

11. A dosage form according to Claim 9 or Claim 10 wherein the proteinoid microspheres include at least one amino acid.

12. A dosage form according to Claim 11 wherein the microspheres include a plurality of amino acids.

13. A dosage form according to Claim 11 wherein the microspheres include at least one diketopiperazine

or at least one mono or di substituted diketopiperazine.

14. A dosage form according to any of Claims 9 to 13 wherein the microspheres comprise diamide-dicarboxylic acids.

15. A dosage form according to Claim 1 or Claim 2 wherein the drug has been converted for transportation into tissues into a form which adapts to its native state within the tissues.

16. A dosage form according to Claim 15 wherein the drug is in an intermediate conformational state between its native and denatured state in a supramolecular complex.

17. A dosage form according to Claim 16 wherein the drug has been converted to said intermediate state by exposure to a complexing perturbant.

18. A dosage form according to any preceding Claim including a mucoadhesive substance.

19. A dosage form according to any preceding Claim in which the solid dispersing form is a low density matrix tablet or water.

20. A dosage form according to Claim 19 wherein the low density matrix is formed by removal of solvent by lyophilisation from a frozen suspension.

21. A dosage form according to Claim 19 wherein the low density matrix is formed by removal of solvent from a frozen suspension by contact with a second solvent, in which the matrix forming materials are insoluble.

22. A dosage form according to Claim 19 wherein the low density matrix is formed by compacting finely divided extruded materials.

23. A dosage form according to Claim 19 wherein the low density matrix is formed by loosely compacting particles formed by spray-coating, spray-drying, lyophilisation, spray-chilling, coacervation, or fluid-bed drying.

24. A dosage form according to Claim 19 wherein the low density matrix is formed by gelling a suspension

and then removing solvent by drying.

25. A dosage form according to any preceding Claim wherein the solid dispensing form disintegrates within 10 seconds in the oral cavity.

INTERNATIONAL SEARCH REPORT

Intern ial Application No
PCT/GB 99/00317

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 26720 A (SCHERER LTD R P ;BREWER FRANCESCA MARY (GB); JOHNSON EDWARD STUART) 6 September 1996 see abstract see page 4, line 31 - page 5, line 14 see page 5, line 33 - page 8, line 31 see claims 1,2,10-14	1,18-21, 24,25
X	EP 0 371 466 A (SCHERING CORP) 6 June 1990 see abstract see page 2, line 13-25 see page 2, line 38-43 see page 3, line 14-17 see claim 6	1,2

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
9 June 1999	16/06/1999

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 866 046 A (AMER MOH S) 12 September 1989 see abstract see column 1, line 45-47 see column 2, line 22-29 see column 2, line 41-48 see column 4, line 18-28 see column 4, line 47-53 see claims 1,8	1,18,25
X	US 5 384 124 A (COURTEILLE FREDERIC ET AL) 24 January 1995 see abstract see column 1, line 64 - column 2, line 21 see column 5, line 62-65 see column 6, line 30-51 see column 9, line 13-14 see claims 1-4	1,2,18, 20
X	WO 93 23017 A (JANSSEN PHARMACEUTICA INC) 25 November 1993 see abstract see page 3, line 12-18 see page 3, line 31 - page 5, line 2 see claims 9,13,15	1,18,19, 21
P,X	WO 98 06379 A (EMBLETON JONATHAN KENNETH ;SCHERER LTD R P (GB)) 19 February 1998 see abstract see page 3, line 31 - page 4, line 21 see page 5, line 2 - page 7, line 8 see claims	1,19,20
X	WO 96 33699 A (EMISPHERE TECH INC ;MILSTEIN SAM J (US)) 31 October 1996 see abstract see page 3, line 13 - page 4, line 12 see page 8, line 26 - page 9, line 11 see page 12, line 26 - page 13, line 2 see claims 15,16,22,24	1,2,9,14
X	EP 0 711 547 A (FUISZ TECHNOLOGIES LTD) 15 May 1996 see abstract see page 2, column 1, line 53-55 see page 3, column 4, line 38-42 see page 4, column 5, line 45-48 see page 4, column 5, line 58 - page 4, column 6, line 7 see page 5, column 7, line 29-31 see page 9, column 15, line 16-39 see page 10, column 18, line 19-42	1,22

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INTERNATIONAL SEARCH REPORT

Interr nal Application No
PCT/GB 99/00317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 587 180 A (ALLEN JR LOYD V ET AL) 24 December 1996 cited in the application see the whole document	1,19,23, 25
X	EP 0 651 997 A (YAMANOUCHI PHARMA CO LTD) 10 May 1995 cited in the application see the whole document	1,2,19, 24,25
X	WO 96 25921 A (NANOSYSTEM LLC) 29 August 1996 cited in the application see abstract see page 1, line 8 - page 2, line 31 see page 6, line 10-15 see page 7, line 4 - page 8, line 9 see page 19, line 7-30 see page 23, line 12 - page 24, line 33 see claim 1	1-5,7,8, 19
X	WO 96 22766 A (NANOSYSTEMS LLC ;WONG SUI MING (US); NEWINGTON IAN M (GB); LIVERSI) 1 August 1996 cited in the application see abstract see page 4, line 17-21 see page 13, line 30 - page 14, line 3 see page 20; table see claim 1	1,3-6
X	US 5 540 939 A (MILSTEIN SAM J ET AL) 30 July 1996 cited in the application see abstract see column 2, line 23-31 see column 3, line 49-67 see column 5, line 43 - column 6, line 8 see column 6, line 12-28 see examples 5,7,8 see claims 1,8,9	1,2,9,10
X	WO 96 09813 A (EMISPHERE TECH INC ;MILSTEIN SAM J (US)) 4 April 1996 cited in the application see abstract see page 3, line 10-27 see page 4, line 24 - page 5, line 8 see page 12, line 31 - page 13, line 10 see page 14, line 14-33 see example 26 see claims 1,3,7-10,28-30	1,2,9, 11-13

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INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/GB 99/00317

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 96 12475 A (EMISPHERE TECH INC ;MILSTEIN SAM J (US); BARANTSEVITCH EVGUENI (US) 2 May 1996 cited in the application see abstract see page 5, line 20 - page 7, line 9 see page 13, line 10-26 see page 45, line 33 - page 46, line 18 see examples 2,3 see claims 1,5,6,13-15,17	1,2, 15-17,19

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INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/GB 99/00317

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. [X] Claims Nos.: –
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

In view of the broad spectrum of compounds or formulations defined by the expressions "matrix", "non-absorbed drug form", "pre-gastric absorption", the search has been restricted to the general concept of fast-dispersing oral dosage forms, to the drug forms defined in claims 3-17, to proceses defined in claims 20-24 and to the relevant IPC groups concerned (PCT Search Guidelines PCT/GL/2 Chapter III, 2.1, 3.6 and 3.7) for economic reasons.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter nal Application No
PCT/GB 99/00317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9626720 A	06-09-1996	AU 702161 B	18-02-1999
		AU 4884696 A	18-09-1996
		BG 101937 A	31-07-1998
		BR 9607057 A	09-06-1998
		CA 2214026 A	06-09-1996
		CZ 9702705 A	14-01-1998
		EP 0814789 A	07-01-1998
		JP 10506409 T	23-06-1998
		NO 974010 A	30-10-1997
		NZ 302723 A	27-04-1998
		PL 322046 A	05-01-1998
		SK 115897 A	04-03-1998
		ZA 9601735 A	18-11-1996
EP 0371466 A	06-06-1990	US 5073374 A	17-12-1991
		AU 631584 B	03-12-1992
		AU 4665489 A	26-06-1990
		CA 2004033 A	31-05-1990
		DK 92991 A	16-05-1991
		EP 0446298 A	18-09-1991
		JP 4502318 T	23-04-1992
		WO 9006136 A	14-06-1990
		US 5112616 A	12-05-1992
US 4866046 A	12-09-1989	WO 9100096 A	10-01-1991
US 5384124 A	24-01-1995	FR 2634376 A	26-01-1990
		US 5417985 A	23-05-1995
		AT 82118 T	15-11-1992
		AU 626031 B	23-07-1992
		AU 3881989 A	25-01-1990
		DK 360489 A	22-01-1990
		EP 0352190 A	24-01-1990
		ES 2052947 T	16-07-1994
		FI 893504 A,B,	22-01-1990
		GR 3006518 T	30-06-1993
		IE 64907 B	20-09-1995
		JP 2088520 A	28-03-1990
		JP 2812723 B	22-10-1998
		KR 146960 B	17-08-1998
		NO 178526 B	08-01-1996
		PT 91237 A,B	08-02-1990
WO 9323017 A	25-11-1993	AU 677198 B	17-04-1997
		AU 4232293 A	13-12-1993
		BG 99158 A	31-05-1995
		CA 2135062 A	25-11-1993
		CN 1085081 A	13-04-1994
		CZ 9402654 A	15-02-1995
		EP 0642334 A	15-03-1995
		FI 945198 A	04-11-1994
		HU 68224 A	28-06-1995
		HU 9500465 A	28-12-1995
		IL 105553 A	04-01-1998
		JP 7508019 T	07-09-1995
		NO 944207 A	04-11-1994
		NZ 252526 A	26-09-1995
		PL 172354 B	30-09-1997

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Interr...nal Application No
PCT/GB 99/00317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9323017 A		SG 47430 A	17-04-1998
		SK 132094 A	11-07-1995
		US 5558880 A	24-09-1996
		US 5648093 A	15-07-1997
WO 9806379 A	19-02-1998	AU 3777897 A	06-03-1998
WO 9633699 A	31-10-1996	US 5820881 A	13-10-1998
		AU 5734096 A	18-11-1996
		CA 2219454 A	31-10-1996
		GB 2314508 A,B	07-01-1998
EP 0711547 A	15-05-1996	US 5567439 A	22-10-1996
		CA 2161752 A	05-05-1996
		JP 8301751 A	19-11-1996
		US 5733577 A	31-03-1998
		US 5851552 A	22-12-1998
		US 5853762 A	29-12-1998
US 5587180 A	24-12-1996	US 5595761 A	21-01-1997
		AU 680345 B	24-07-1997
		AU 1688595 A	15-08-1995
		BG 100749 A	28-02-1997
		BR 9506579 A	16-09-1997
		CA 2181990 A	03-08-1995
		CN 1139877 A	08-01-1997
		CZ 9602068 A	11-12-1996
		EP 0743850 A	27-11-1996
		FI 962989 A	26-07-1996
		HU 74514 A	28-01-1997
		JP 9511489 T	18-11-1997
		NO 963140 A	25-09-1996
		NZ 279674 A	24-02-1997
		PL 315685 A	25-11-1996
		SG 46962 A	20-03-1998
		SK 91096 A	04-06-1997
		WO 9520377 A	03-08-1995
		US 5807576 A	15-09-1998
		ZA 9500677 A	08-05-1996
EP 0651997 A	10-05-1995	AU 3095992 A	28-07-1993
		DE 69227467 D	03-12-1998
		DE 69227467 T	22-04-1999
		FI 943042 A	23-06-1994
		JP 2807346 B	08-10-1998
		NO 942403 A	24-08-1994
		US 5466464 A	14-11-1995
		AT 172637 T	15-11-1998
		CA 2126669 A	08-07-1993
		HU 75455 A	28-05-1997
		WO 9312769 A	08-07-1993
		NZ 246091 A	28-08-1995
WO 9625921 A	29-08-1996	US 5565188 A	15-10-1996
		AU 5025596 A	11-09-1996
		CA 2213663 A	29-08-1996
		EP 0810855 A	10-12-1997
		JP 11500733 T	19-01-1999

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intern tal Application No
PCT/GB 99/00317

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9625921 A		US 5705194 A	06-01-1998
WO 9622766 A	01-08-1996	US 5569448 A	29-10-1996
		AU 4368296 A	14-08-1996
US 5540939 A	30-07-1996	US 5401516 A	28-03-1995
		AU 6017194 A	19-07-1994
		AU 6668594 A	08-11-1994
		CA 2151818 A	07-07-1994
		CA 2160692 A	27-10-1994
		CN 1094611 A	09-11-1994
		EP 0674507 A	04-10-1995
		EP 0696192 A	14-02-1996
		JP 8507043 T	30-07-1996
		JP 8509231 T	01-10-1996
		MX 9400166 A	29-07-1994
		WO 9414420 A	07-07-1994
		WO 9423702 A	27-10-1994
		ZA 9309608 A	24-08-1994
		ZW 17893 A	27-07-1995
WO 9609813 A	04-04-1996	US 5693338 A	02-12-1997
		AU 4129396 A	19-04-1996
		US 5714167 A	03-02-1998
WO 9612475 A	02-05-1996	US 5714167 A	03-02-1998
		AU 4152496 A	15-05-1996
		EP 0781124 A	02-07-1997
		JP 10509433 T	14-09-1998